CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 75-318

Trade Name: Ticlopidine Hydrochloride Tablets 250mg

Generic Name: Ticlopidine Hydrochloride Tablets 250mg

Sponsor: Invamed Inc.

Approval Date: August 20, 1999

INDICATION(s): to reduce the risk of thrombotic stroke (fatal or non-fatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke.

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Approvable Letter	X			
Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
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APPROVAL LETTER

AUG 2 0

ANDA 75-318

Invamed, Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130 N
Dayton, NJ 08810

Dear Sir:

This is in reference to your abbreviated new drug application dated January 21, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ticlopidine Hydrochloride Tablets, 250 mg.

Reference is also made to our approvable letter dated May 4, 1999, and to your amendments dated June 28, July 27, August 7, and August 13, 1999.

The listed drug product (RLD) referenced in your application, Ticlid Tablets of Syntex U.S.A. Inc., is subject to a period of patent protection which expires on May 27, 2003 (U.S. patent 4,591,592 [the '592 patent]. Your application contains a patent certification to the '592 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on the patent. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified the Agency that Invamed, Inc. (Invamed) has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Invamed within the statutory forty-five day period. However, the agency has been precluded from granting final approval to your application because of the eligibility for 180-day generic drug exclusivity granted to TorPharm, Inc. concurrently with the approval of their abbreviated application for Ticlopidine Hydrochloride Tablets, 250 mg, on July 1, 1999.

Further reference is made to litigation [Teva Pharmaceuticals

USA, Inc; Purepac Pharmaceutical Co.; and Invamed, Inc. v. United States Food and Drug Administration; TorPharm, a Division of Apotex, Inc.; and Hoffman-LaRoche, Inc. and Syntex (U.S.A.), Inc.] in the United States District Court for the District of Columbia, Civil Action No. 99-67 (CKK) in which the court entered a final judgement on August 18, 1999, in favor of the plaintiffs. This ruling effectively voided the agency's award of 180-day generic drug exclusivity to TorPharm, Inc. Additional reference is made to two unsuccessful appeals of this decision made by the defendants to both the district and appeals court level.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ticlopidine Hydrochloride Tablets, 250 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ticlid® Tablets, 250 mg of Syntex U.S.A., Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

We note that Invamed has committed to provide a post-approval educational program that will be implemented upon the distribution and marketing of Ticlopidine Hydrochloride Tablets that incorporates the following elements:

1. Target audience for an adequate educational campaign.

    a. Physicians, including those within a health-care system such as an HMO or PPO, who prescribe Ticlopidine.

    b. Other health-care professionals, such as nurse practitioners, physician assistants, and dispensing pharmacists, who are in a position in a given health-care system to educate patients and/or monitor compliance.

2. Substantive elements of an adequate educational campaign.

    a. A clear statement that Ticlopidine is approved for use only in patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.

    b. Discussion of the known risks of Ticlopidine therapy and how to mitigate them. An adequate discussion would include not only information about the frequency and

potential severity of adverse events, but also information about the role that clinical observation and blood monitoring can play in preventing/minimizing their clinical severity. The discussion should include information about the following known adverse events:

(i) Neutropenia/agranulocytosis;

(ii) Thrombotic thrombocytopenic purpura (TTP); and

(iii) Aplastic anemia.

c. Information delineating the schedule for blood and clinical monitoring during the first three months of treatment, and describing the steps to be taken should the results of such monitoring be abnormal.

d. A statement reinforcing the need for all health-care professionals to report observed serious and fatal adverse events with Ticlopidine administration to MedWatch.

Invamed plans to implement this program by the following means:

1. Direct mailing to key physicians, pharmacists, and other health-care professionals.

2. Publication of educational information in selected, well recognized medical journals targeting health-care professionals who are in a position, in a given health-care system to educate patient and/or monitor compliance.

3. A web site providing on-line, continuing educational information. The web site address will be referenced in the direct mailing and publications.

Invamed also commits to provide, at the time of product marketing, details of the educational program plan. This report will cover the range of activities that constitute the program and will include items such as timelines, target audiences and the modes of dissemination of the educational materials, web site identification, and copies of extant educational materials. In addition, Invamed commits to provide a brief summary of the implementation efforts, as well as any other relevant data, associated with the educational program in each annual report.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

8/20/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER :

APPROVABLE LETTER

ANDA 75-318

MAY 4 1999

Invamed, Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130 North
Dayton, NJ 08810

Dear Sir:

This is in reference to your abbreviated new drug application dated January 21, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ticlopidine Hydrochloride Tablets, 250 mg.

Reference is also made to your amendments dated July 2, July 10, and October 21, 1998; and February 5, and May 1, 1999.

We have completed the review of this abbreviated application as submitted and have concluded that it is approvable. However, before the application may receive a tentative approval, additional information may be needed about your proposed educational program to assure that adequate precautions have been taken for the safe marketing of the drug product.

We note that we have no record of receiving a detailed discussion of your proposed educational plan in response to our September 21, 1998, letter. The agency is currently considering whether such a program is necessary and what elements, if any, should be included in a program designed to educate health professionals about the appropriate use of the drug product. The agency expects to complete its review shortly. Notice of the outcome of this review will be provided to all applicants of this drug product.

Within 10 days after you receive the agency's notice referred to above, if additional information is needed, you will be required to amend this application, or follow one of the other options under 21 C.F.R. § 314.110. In the absence of such action, FDA will refuse to issue a tentative approval or approval letter. This submission should be clearly designated in bold print as a **MINOR AMENDMENT** in your cover letter.

Please note that an abbreviated application for Ticlopidine Hydrochloride Tablets, 250 mg, containing a Paragraph IV Certification was previously accepted for filing by this office prior to the receipt of your application. Accordingly, after amendment, if any, your application will be eligible for final approval beginning on the date that is one hundred and eighty (180) days after the first commercial marketing of the drug product under the previous application, or the date of a court decision described under Section 505(j)(5)(B)(iv), whichever occurs first. We refer you to the Agency's recently issued guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

Any changes in the conditions outlined in this abbreviated application or the status of the manufacturing and testing facilities' compliance with current good manufacturing practice (CGMP) procedures are subject to Agency review before final approval of the application will be made.

This drug product may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act and 21 U.S.C. § 331(d). Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list (commonly referred to as the "Orange Book").

Prior to submitting the amendment, please contact Robert L. West, Director, Division of Labeling and Program Support, at (301) 827-5846, for further instructions.

Sincerely yours,

/S/ 5/4/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research